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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,738	11/12/2003	John Hilfinger	TSR-10002/38	7532

25006 7590 04/17/2007

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,738	HILFINGER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16,19,20,22,24,26,27 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16,19,20,22,24,26,27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/28/07 has been entered.

Claims 17, 18, 21, and 23 were canceled as requested.

Claims 8-16, 19, 20, 22, 24, 26, 27, and 30 remain pending and are under consideration.

Rejections not reiterated from the previous Office Action are withdrawn.

Specification

The amendment filed 2/20/07 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In the paragraph beginning at line 15 of page 9, Applicant has deleted cholic acid from the specific examples of inventive cholesterol derivatives. This constitutes new matter by deletion. In the specification as filed it was clear that cholic acid was considered to be a specific example of an inventive cholesterol derivative. Deletion of cholic acid from the list of

derivatives in the specification is new matter because it represents a change to what Applicant considered to be the invention at the time of filing in view of the specification as filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012).

Niedzinski taught cholic acid conjugates comprising a polyamine DNA binding domain, their use to protect DNA from degradation in the gastric system, and their use to deliver plasmids to NIH 3T3 cells in vitro. Niedzinski envisioned the use of these conjugates to deliver therapeutic nucleic acids by oral delivery to the gastrointestinal system, particularly to the enterohepatic receptors of the small intestine, which are specific for bile salts. See abstract, paragraph bridging pages 721 and 722. The cholic acid moieties were esterified through an oxygen at C3 to a DNA binding domain, or through a carboxylic acid moiety corresponding to that present on bile acids. See scheme 1, compound 5 or 6, page 722.

Niedzinski did not teach the use of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, or taurochenodeoxycholic acid. However, Niedzinski considered his conjugation technique to be applicable to a variety of bile acids (see last sentence of column 1 on page 724), and it was clear that it could be applied to either the C3 hydroxyl, so the presence of a carboxyl group was not required.

Keener taught the use of bile acids, and cholesterol derivatives generally, as hydrophobic conjugates to aid in the cellular entry of a conjugated peptide (proricin). Bile acids and cholesterol derivatives included cholic acid, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, and taurocholic acid. See column 19, lines 37-55. Thus it was clear to one of ordinary skill in the art at the time of the invention that bile acids and cholesterol derivatives were equivalent alternative hydrophobic groups in the art of conjugating hydrophobic groups to compounds intended for delivery to cells.

It would have been obvious to one of skill in the art at the time of the invention to substitute any hydrophobic bile acid or cholesterol derivative for the cholic acid of Niedzinski. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on

its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Niedzinski also did not teach peptide DNA binding domains.

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of ABZ, wherein A is a steroid such as cholic acid, stigmasterol, or ergosterol, B is a linker, and Z can be a nucleic acid binding domain such as a polyamine or a polycationic peptide (protamine, a histone, or a nucleic acid binding protein). See column 3, lines 50-64; column 4, lines 50-54; column 5, lines 36 and 52-58; and column 9, line 58 to column 10, line 10. Accordingly, it was clear to those of ordinary skill in the art at the time of the invention that it was routine to conjugate nucleic acid binding domains to cholesterol derivatives for nucleic acid delivery, and that acceptable nucleic acid domains included polyamines and polycationic nucleic acid binding peptides such as protamines and histones.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a nucleic acid binding peptide for the nucleic acid binding polyamine of Niedzinski because these nucleic acid binding moieties were recognized in eh art as equivalents. See MPEP 2144.06.

Regarding claim 20 and the 'Y' linker peptide moiety, the first 2 or 3 amino acids of the DNA-binding peptide can be considered to be the linker peptide.

Regarding claim 30, the cited art did not explicitly teach a commercial package comprising the composition and instructions for use. However, Gebeyehu did teach kits

comprising the compositions. See column 13, lines 18-24. it would have been obvious to one of ordinary skill in the art at the time of the invention to place the components of such a kit into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that referring to instructions decreases the frequency of errors. Thus the invention as a whole was prima facie obvious.

Thus the invention as a whole was prima facie obvious.

Claims 11, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002).

Niedzinski, Keener, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by orally administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. The DNA/lipidic agent was also formulated with DOTAP and/or DOPE. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726.

These references were silent as to the secretion of the protein form the target cells, and did not exemplify a composition comprising a therapeutic compound.

Perrie taught oral intragastric delivery of cationic liposome comprising nucleic acids encoding hepatitis B surface antigen (HbsAg). DNA vaccines encoding HbsAg were formulated with cationic lipids (DOTAP) and administered orally. Immune responses against the antigen were observed. See abstract. HbsAg is a surface protein, and so is expressed and routed through the secretory pathway. Also, generation of an immune response requires presentation of the antigen on a cell surface, again requiring secretion.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the conjugate of Niedzinski as modified by Keener and Gebeyehu in the method of Perrie. Niedzinski taught that the lipid could be substituted for, or added to, such cationic lipids as DOTAP. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. Thus the invention as a whole was prima facie obvious.

Claims 15 and 16 are included in this rejection because the nucleic acid of Perrie is considered to be a therapeutic product that is antibiotic in nature by virtue of its activity in inducing an immune response against hepatitis B virus.

Claims 11, 12, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

Niedzinski, Keener, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by orally administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. The DNA/lipidic agent was also formulated with DOTAP and/or DOPE. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726.

These references did not teach secretion of an expressed protein, and did not exemplify a composition comprising a therapeutic compound.

Kitadai taught transfection of human gastric carcinoma cells with an expression vector encoding the secreted protein interleukin-8. Transfection was performed using the cationic lipid formulation LIPOFECTIN (DOTMA/DOPE).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cationic lipid of Niedzinski as modified by Keener and Gebeyehu in the method of Kitadai. Niedzinski taught that the lipid could be substituted for, or added to, such cationic lipids as DOTMA and DOPE. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726. MPEP 2144.06 indicates that when it is

recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Claims 15 and 16 are included in this rejection because the nucleic acid of Kitadai is considered to be a therapeutic product that is an antitumoral.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

(Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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Art Unit 1635